

### **Amendments to the Specification**

Please insert the following paragraph right after the title on page 1:

#### **--RELATED APPLICATIONS**

This is a National Stage Application of International Application  
PCT/GB02/01137, filed December 3, 2001.--

Please amend the specification at page 1, line 26 to read as follows:

--The most often used clinical diagnostic criteria are the NINCDS/ADRDA criteria (McKhann, G. et al., (1984) Neurology 34: 939-944), originally designed for research purposes. These criteria are highly sensitive but have a low specificity. This is due to the fact that the positive predictive value of a diagnosis of "probable" or "possible" Alzheimer's disease is very high, but the negative predictive value is very low (13). In other terms, if a patient fulfils the requirements of the NINCDS/ADRDA criteria for Alzheimer's disease it is highly likely that the patient indeed has got Alzheimer's disease. However, a proportion of the patients who do not ~~fulfil~~ fulfill these criteria (e.g. are regarded as controls) are found to have Alzheimer's disease at post mortem examination (13).--

Please amend the specification at page 2, line 30 to read as follows:

-- Studies by the present ~~inventors~~ inventor and others indicate that the cell cycle regulatory failure in Alzheimer's disease occurs at the G1/S transition checkpoint (3). Previous studies on fibroblasts and lymphocytes from Alzheimer's disease patients indicate that the regulation of the cell division cycle might be disrupted in cells other than neurons in this condition (8, 9, 17). It is also known that Alzheimer's disease patients are more prone to some forms of cancer (4) and that Down's syndrome patients, who develop AD in early adult life, are more prone to leukaemia than the general population (7, 10). It is plausible therefore to ~~hypothesise~~ hypothesis that the cell cycle regulatory failure in neurons, even in early (pre-clinical) stages of AD, might be reflected by similar cell cycle regulatory malfunction in lymphocytes.--

Please amend the specification at page 3, line 10 to read as follows:

--The present ~~inventors~~ inventor have now shown that the in vitro responsiveness of lymphocytes to G1 inhibitor treatment is significantly less effective in Alzheimer's disease patients than in control subjects. Additionally, in subjects showing clinical signs of incipient

Alzheimer's disease the lymphocyte-response is similar to that seen in Alzheimer's disease patients. These findings represent direct evidence to support the hypothesis that the failure of the G1/S transition control is not restricted to neurons in Alzheimer's disease patients, but also occurs in peripheral cells, such as lymphocytes.--

Please amend the specification at page 4, line 33 to read as follows:

--The availability of a reliable test for a defect underlying the pathology of Alzheimer's disease will significantly improve the ability to diagnose the condition, and in particular will enable early diagnosis. The currently available operational diagnostic criteria for Alzheimer's disease only allow diagnosis of possible or probable AD very late, when dementia is already present. A definite diagnosis of Alzheimer's disease can only be made after post mortem examination. It is apparent from the work of the present ~~inventors~~ inventor that a defect in cell cycle control is detectable in peripheral (non-neuronal) cells, such as lymphocytes, well before the clinical signs of fully developed dementia appear. Hence, the method of the invention provides a tool for early diagnosis of Alzheimer's disease, especially detection of individuals who are in pre-clinical stages of the disease, and for identification of individuals who have not yet developed Alzheimer's disease as such but are "at risk" of doing so because of the presence of the cell cycle regulatory defect. This opens up the possibility of early intervention with preventive measures, including, *inter alia*, changes in life style and vitamin regimes and HRT for post menopausal women.--

Please amend the specification at page 23, line 19 to read as follows:

--The study included 102 subjects who were full participants of the Oxford Project to Investigate Memory and Ageing (OPTIMA). The yearly routine OPTIMA examination includes a physical examination, cognitive and neuropsychological testing. Drug intake and any intercurrent infections are recorded. Blood was collected in lithium heparin or EDTA vacutainers. Lymphocytes were isolated according to a standard protocol using ~~Ficall~~ Ficoll (Sigma). In order to ~~standardise~~ standardize the culture methods for all patients the separated lymphocytes were frozen and stored for further analysis.--

Please amend the specification at page 25, line 21 to read as follows:

--The results were ~~analysed~~ analyzed in relation to the clinical diagnosis provided by the clinicians involved in the OPTIMA project.--

Please amend the specification at page 28, line 2 to read as follows:

--In this study the effects of a specific G1 inhibitor (rapamycin) (16, 19) on the length of the G1 phase in lymphocytes were ~~analysed~~ analyzed using BrdU incorporation assay and FACS analysis. The reduction of cell numbers in the cultures following rapamycin treatment was also assessed. In a second approach, G1 inhibition was elicited by oxidative stress and the reduction of cell numbers in the culture system measured.--